Complete Summary

GUIDELINE TITLE

Stem cell transplantation in adults: recommendations.

BIBLIOGRAPHIC SOURCE(S)

Imrie K, Rumble RB, Crump M, Advisory Panel on Bone Marrow and Stem Cell Transplantation, Hematology Disease Site Group. Stem cell transplantation in adults: recommendations. Toronto (ON): Cancer Care Ontario Program in Evidence-based Care; 2009 Jan 30. 78 p. (Recommendation report; no. 1). [66 references]

GUIDELINE STATUS

This is the current release of the guideline.

The Recommendation Report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Indications that may require stem cell transplantation, including:

- Acute lymphoblastic leukemia (ALL) (including lymphoblastic lymphoma)

- Acute myeloid leukemia (AML)
- Acute promyelocytic leukemia (APL)
- Aplastic anemia (AA)
- Chronic lymphocytic leukemia (CLL)
- Chronic myeloid leukemia (CML)
- Hodgkin's lymphoma (HL)
- Multiple myeloma (MM)
- Myelodysplastic syndrome (MDS)
- Non-Hodgkin's lymphomas
    - Aggressive histology non-Hodgkin's lymphoma (NHL) including diffuse large B cell lymphoma and aggressive T cell lymphomas (AH-NHL)
    - Follicular lymphoma (FL)
    - Burkitt's lymphoma
    - Mantle cell lymphoma (MCL)
- Solid tumours

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Evaluation
Management
Treatment

CLINICAL SPECIALTY

Hematology
Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To guide policy makers in their decision making regarding the indications for stem cell transplantation
- To inform clinical decision making regarding the appropriate role of stem cell transplantation and to guide priorities for future research
- To specifically address the following:
    - The accepted indications for stem cell transplantation
    - What measures are commonly reported to assess transplant outcomes
    - The published standards guiding performance of transplantation

TARGET POPULATION

All adult cancer patients being considered for treatment that includes either bone marrow or stem cell transplantation

INTERVENTIONS AND PRACTICES CONSIDERED

1. Allogeneic stem cell transplantation

2. Autologous stem cell transplantation
3. Measures to assess transplant outcome and performance

MAJOR OUTCOMES CONSIDERED

- Stem cell transplantation-related morbidity and mortality
- Survival (overall, disease-free, event-free, relapse-free)

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Literature Search Strategy

Using OVID, the MEDLINE (1996 through January [week 4], 2008), EMBASE (1996 through week 5, 2008), and Cochrane Database of Systematic Reviews (CDSR) (through December 31, 2007) databases were searched for evidence. For the MEDLINE and EMBASE searches, terms for bone marrow transplantation were combined with terms for stem cell transplantation, autologous and allogeneic transplantation, the various diseases included, and evidence-based medicine (EBM) publication types. These results were then limited to the English language, reports on human subjects, and reports published after 1999. The search terms varied depending on the database being used, and the search strategies used appear in Appendix 2 and 3 in the original guideline document. A flow diagram of the literature search appears in Appendix 4 in the original guideline document.

An environmental scan of the non-indexed evidence was also performed on October 26, 2007. The environmental scan was comprised of two parallel processes, one a targeted search of known organizations that produce evidence-based medicine products and the other an untargeted search to identify previously unknown sources of evidence. A listing of the organizations that were examined in the targeted search is given in Appendix 5 in the original guideline document. For the untargeted search, the Google™ online internet search engine was used with the keywords "bone marrow transplantation" + "guideline", "bone marrow transplantation" + "standards", "stem cell transplantation" + "guideline", and "stem cell transplantation" + "standards."

Evidence Selection Criteria

The types of evidence eligible for inclusion in this review were:

1. Existing evidence synthesis and summary reports, including clinical practice guidelines, systematic reviews with or without meta-analyses, review articles, technology assessments, consensus statements, and standards documents.

2. Published papers discussing indications where stem cell transplantation (SCT) is appropriate (including disease site/state; any data on proven indications if available).
3. Published papers of short and long term outcomes, current and proposed models for monitoring, and quality planning/improvement.

Excluded Evidence

Papers reporting on non-malignant disease were excluded. The Panel is aware that SCT is performed in adults for non-malignant indications such as myeloproliferative disorders, immune deficiency syndromes, and hemoglobinopathies but is also aware that these indications account for a very small proportion of the transplants performed in Ontario and other jurisdictions and that, therefore, evidence on which to base recommendations is extremely limited.

NUMBER OF SOURCE DOCUMENTS

53 articles were included.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

As the evidence review was intended to locate summary documents of evidence and recommendations, and not clinical trial reports themselves, no pooling was planned or performed.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Recommendations Development

Initial Draft Recommendations and Panel Review

The initial recommendations were drafted by two clinical experts designated by the Panel and the Hematology Disease Site Group (DSG) as the lead clinicians for the project. They were drafted to be evidence-based to the greatest extent feasible, given the evidence review.

The Panel then reviewed the draft recommendations and the evidence review and provided feedback. This discussion and the Panel's evaluation of the evidence and recommendations is summarized above in the "Discussion of Evidence Review" section of the original guideline document.

Hematology Disease Site Group (DSG) Consensus

In order that this document be fully completed and made available to the clinical community of Ontario, a decision was made by the Panel and the Director of the Program in Evidence-Based Care (PEBC) that the document become the responsibility of the Hematology DSG upon completion of the Panel's mandate. The Hematology DSG agreed to take on this responsibility, and the draft document created by the Panel was presented to the Hematology DSG. The Hematology DSG was provided with the full document, including the evidence review and the draft recommendations developed by the Panel. Given the wide variability in the evidence base, and the heavy reliance upon consensus for some indications, the co-chairs of the DSG decided that a formal vote be taken for each of the recommended indications. For each of the indications, an electronic voting system was used to compile DSG responses. All members were asked to approve the draft recommendations as stated or to ask for revisions. The option to decline a vote was offered if some felt they were not qualified to make a decision, which explains the variation in response rates.

The DSG recognized the importance of this document as a means of facilitating equitable access to transplant services across the province but expressed some discomfort with the highly variable nature of the evidence available to inform the recommendations. The DSG noted that, for some indications, recommendations were entirely based on expert opinion, with no available controlled trials. The DSG requested that the quality of evidence supporting the individual recommendations be included in the document. This systematic review is of guidelines and of systematic reviews rather than of the primary studies. A listing of the randomized controlled trials (RCTs) that informed the guidelines has been included in Appendix 6 in the original guideline document.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Advisory Panel on Bone Marrow and Stem Cell Transplantation Consensus

Following presentation of the draft recommendations to the Advisory Panel at the third and final meeting, the entire Panel was polled once more for any additional comments before the document went on to completion. All Panel members approved the recommendations as drafted, with the some exceptions forwarded by two members on three of the included indications, along with some additional commentary of a more general nature.

Refer to the original guideline document for more information about the Advisory Panel approval process.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Indications

The following recommendations address the role of stem cell transplantation for the following indications:

Acute Lymphoblastic Leukemia (ALL) (including lymphoblastic lymphoma)

- *First complete remission*:
  - Allogeneic stem cell transplantation is an option for patients with ALL with poor prognostic features such as Philadelphia chromosome or t(4;11) positivity or delayed time to first complete remission.
  - Autologous stem cell transplantation is not recommended for patients with ALL in first complete remission.
- *Beyond first complete remission*:
  - Allogeneic transplantation is the recommended treatment option for eligible patients with ALL who achieve a second remission.
  - There is insufficient evidence to support or refute the use of autologous stem cell transplantation beyond first remission for patients with ALL.

Acute Myeloid Leukemia (AML)

- *First complete remission*:
  - Allogeneic transplantation is a treatment option for selected patients with AML in first complete remission with high-risk features such as high-risk cytogenetic or molecular phenotypes and secondary AML.
  - Autologous stem cell transplantation is not recommended for patients with AML in first complete remission.
- *Beyond first complete remission*:
  - Allogeneic transplantation is the recommended option for eligible patients with AML who achieve a second or subsequent remission.

- There is insufficient evidence to support or refute the use of autologous stem cell transplantation for patients with AML in the second or subsequent remission.

Acute Promyelocytic Leukemia (APL)

- *First complete remission*:
  - Stem cell transplantation is not recommended for patients with APL in first complete remission.
- *Beyond first complete remission*:
  - There is insufficient evidence to support or refute the use of stem cell transplantation for patients with APL in the second or subsequent remission.

Aplastic Anemia (AA)

- Allogeneic stem cell transplantation is the recommended treatment option for eligible patients under age 30-40 years of age with severe or very severe AA.
- Allogeneic stem cell transplantation is an option for selected patients with severe or very severe AA over the age of 30-40 years of age.
- Autologous stem cell transplantation is not recommended for patients with AA.

Chronic Lymphocytic Leukemia (CLL)

- Allogeneic stem cell transplantation is an option for selected patients with CLL, including those with high-risk cytogenetics who have failed purine analog therapy.
- Autologous stem cell transplantation is not recommended for patients with CLL.

Chronic Myeloid Leukemia (CML)

- Allogeneic stem cell transplantation is an option for patients with CML for whom medical therapy has failed, as well as those in accelerated phase or blast crisis.
- Autologous stem cell transplantation is not recommended for patients with CML.

Hodgkin's Lymphoma (HL)

- Autologous stem cell transplantation is the recommended treatment option for eligible chemosensitive patients with HL who are refractory to or who have relapsed after primary chemotherapy.
- Allogeneic stem cell transplantation is an option for chemosensitive patients with refractory or relapsed HL who are not candidates for autologous stem cell transplantation or who have a syngeneic (identical twin) donor.
- Stem cell transplantation is not recommended as part of primary therapy for HL.

Multiple Myeloma (MM)

- Autologous stem cell transplantation is the recommended treatment option for eligible younger patients (under age 65-70 years) with newly diagnosed MM.
- Tandem (double) autologous stem cell transplantation is an option for patients who obtain less than a complete response to the first autologous transplant.
- Repeat autologous transplantation is an option for patients with MM who relapse after a long remission (> 2 years) to a single autologous transplant.
- Allogeneic transplantation is an option for selected patients with MM including those with high-risk cytogenetics and those whose disease is unresponsive to primary therapy.

Myelodysplastic Syndrome (MDS)

- Allogeneic transplantation is an option for selected patients with MDS.
- Autologous stem cell transplantation is not recommended for patients with MDS.

The Non-Hodgkin's Lymphomas (NHLs)

Aggressive Histology NHL Including Diffuse Large B Cell Lymphoma and Aggressive T Cell Lymphomas (AH-NHL)

- Autologous stem cell transplantation is the recommended option for eligible chemosensitive patients with AH-NHL refractory to or relapsed after primary therapy.
- Allogeneic stem cell transplantation is an option for eligible chemosensitive patients with refractory or relapsed AH-NHL who are not candidates for autologous stem cell transplantation or who have a syngeneic (identical twin) donor.
- Stem cell transplantation is not recommended for patients with AH-NHL as part of primary therapy.

Follicular Lymphoma (FL)

- Autologous or allogeneic transplantation are options for selected patients with poor prognosis FL that progresses after second-line therapy.

Burkitt's Lymphoma

- Autologous and allogeneic transplantation are options for selected patients with Burkitt's lymphoma beyond first remission.
- Stem cell transplantation is not recommended for patients with Burkitt's lymphoma in first complete remission.

Mantle Cell Lymphoma (MCL)

- Autologous stem cell transplantation is an option for eligible patients with MCL in first remission.
- Autologous or allogeneic transplantation are options for selected patients with MCL in second remission.

Solid Tumours

- Autologous stem cell transplantation (single or tandem) is a treatment option for patients with gonadal or retroperitoneal germ cell tumours refractory to or relapsed after cisplatin-based chemotherapy.
- Stem cell transplantation is not recommended in patients with other solid tumours including breast, ovarian, and lung cancers.

Assessment and Performance

The following recommendations address what measures should be assessed when reporting transplant outcomes:

Measures to Assess Transplant Outcomes

- Treatment-related mortality
- Relapse-free survival
- Disease-free survival
- Event-free survival
- Outcome at 12 months and annual follow-up: current survival status (alive/dead/unknown), current disease status (refractory, response, relapse), further treatment since initial treatment program (yes/no)
- Overall survival (including date of death, cause of death)

Demographic Information

- Patient identification: date of birth, postal code, sex (male/female), Ontario Health Insurance Plan (OHIP) number, General Practitioner's name

Procedure Information

- Immediate plan for transplantation versus (vs.) deferred ("rainy day") harvest (yes/no; date collected)
- Autograft (yes/no; date)
- Allograft (yes/no; date)

The following recommendations address published standards guiding performance:

Published Standards Guiding Performance

- Treatment-related mortality is a reliable measure of performance between centres.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by clinical practice guidelines;Â review articles;Â reviews with an expert panel consensus; systematic reviews; position statements, consensus statements, monographs, or special reports; technology assessments; meeting reports or grand rounds reports; and database audits using population-based data.

Where possible, the Advisory Panel on Bone Marrow and Stem Cell Transplantation (the Panel) and the Hematology Disease Site Group (DSG) developed these recommendations on the basis of clinical trial evidence identified in this review. In the absence of clinical trial evidence, the Panel and the Hematology DSG developed recommendations through the consensus of world opinion shown by the identified documents, as well as their own expert opinion.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Accurate identification of accepted indications for stem cell transplantation

POTENTIAL HARMS

Stem cell transplantation is associated with significant toxicity and transplant-related mortality.

CONTRAINDICATIONS

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Acute Lymphoblastic Leukemia (ALL)

- The evidence reviewed does not support high dose chemotherapy and allogeneic stem cell transplantation (SCT) as salvage treatment after relapse or progression following high dose chemotherapy and autologous SCT in patients with ALL.
- SCT is not recommended as a treatment option during first complete remission (CR).

Acute Myeloid Leukemia (AML)

While autologous bone marrow transplantation (BMT) may hold less risk than allogeneic BMT, survival is also poorer.

Hodgkin's Lymphoma (HL)

There is no evidence to support allogeneic SCT at this time.

Multiple Myeloma (MM)

There are no data supporting high-dose chemotherapy (CT) with SCT for patients over 70 years and the combination of melphalan and prednisone should remain the standard treatment.

Myelodysplastic Syndrome (MDS)

- For older patients who may have a life-expectancy of five to 10 years, conservative chemotherapy (CT) therapy may be a more appropriate treatment option.
- Autologous BMTÂ is less risky than allogeneic BMT but has poorer survival, and therefore cannot be recommended at this time.

Solid Tumors

- High-dose CT with autologous SCT has no demonstrated efficacy in advanced epithelial ovarian cancer, primary breast cancer, small-cell lung cancer, or germ-cell tumours.
- There is also no benefit for high-dose CT with autologous BMT in patients with breast cancer compared with standard-dose CT alone.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- The role of BCR-ABL inhibitors (e.g., imatinib, dasatinib) in the management of Philadelphia chromosome positive acute lymphoblastic leukemia (ALL) is currently being explored as therapy prior to or following allogeneic transplantation.
- In the management of aplastic anemia, the choice of stem cell transplantation or immunosuppressive therapy with agents such as antithymocyte globulin (ATG) and cyclosporine must take into consideration the expected toxicities of the two treatments as well as patient preference.
- The management of chronic lymphocytic leukemia (CLL) is in evolution with the emergence of new treatment options, including targeted therapy. These options must be considered when recommending stem cell transplantation.
- Evidence on the role of stem cell transplantation in the management of multiple myeloma (MM) is rapidly emerging. This topic is the subject of Program in Evidence-based Care Evidence-based Series #6-6, which will be updated to incorporate new data.
- The choice of whether to use an autologous or allogeneic procedure must be made by the patient in consultation with his/her clinician in consideration of the expected benefits and harms associated with each procedure in this disease setting.
- Age is generally considered a surrogate for co-morbidity as toxicity and treatment-related mortality with transplantation increase with age.
- Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician.

Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Imrie K, Rumble RB, Crump M, Advisory Panel on Bone Marrow and Stem Cell Transplantation, Hematology Disease Site Group. Stem cell transplantation in adults: recommendations. Toronto (ON): Cancer Care Ontario Program in Evidence-based Care; 2009 Jan 30. 78 p. (Recommendation report; no. 1). [66 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2009 Jan

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Hematology Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

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GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

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